**End-Stage Liver Disease, Upper GI Bleeding and
Coagulopathy in the Critically Ill Patient**

John W. Schweiger, M.D.   Tampa, Florida

OBJECTIVES

(1) Develop a basic understanding of the pathophysiology of end-stage liver disease (ESLD),

(2) Develop an appreciation of the pathophysiology, as well as the initial management of hepato-pulmonary, and hepato-renal syndromes,

(3) Develop a basic understanding of the diagnosis & pathophysiology of severe generalized (i.e., non-surgical) bleeding in adults, and

(4) Develop an organized strategy to the management of disseminated intravascular coagulopathy (DIC) with special emphasis on the rational use of blood & blood component therapy

STEM CASE - KEY QUESTIONS

The patient is a 55 y.o. male who presented to the ER with a chief complaint of "spitting up blood for three days." He states that he was in his "usual state of poor health" until about one week ago when he went on a 24 hour drinking binge. At the conclusion of this ordeal, the patient lost consciousness for "about 16 hours." The next day, he noticed one large episode of vomiting, followed by several smaller ones that were blood-tinged. Over the past 24 hrs, he had begun to feel "extremely light-headed and almost passed out prior to coming to the ER."

His past medical history includes: (1) Hepatitis B x 25 yrs, (2) HTN x 15 yrs, (3) COPD / emphysema x 10 yrs, and (4) Alcoholic Cirrhosis x 5 yrs (several intermittent episodes of pancreatitis). The surgical history contains; (1) S/P exploratory laparotomy - sustained after a MVA at age 27 y.o., (2) S/P laparoscopic cholecystectomy (age 45 y.o.), (3) S/P EGD with electrocautery (age 50 y.o.), and (4) S/P TIPSS procedure (age 54 y.o.). His allergies include; (1) ASA & NSAID - upper & lower GI bleeding, and (2) Naltrexone - "freaking out". The medical regimen; (1) Albuterol + Atrovent + Beclomethasone MDI's, (2) Methadone tabs PO TID, (3) Propranolol caps PO BID, (4) Spironolactone caps PO BID, and (5) Valium prn.

The patient reports that he was adopted and is not aware of his family Hx. He currently lives on social security / disability income. On questioning, the patient admits to consuming 8-to-10 twelve oz. beers per day, as well as occasionally drinking 2-to-3 glasses of "hard liquor" per day. In addition, he smokes 2-to-3 packs of cigarettes per day, and rarely uses cocaine and/or marijuana, although he was a "heavy consumer" in the past.

He is 6' 02" tall, and weighs 72 kg. His vital signs include a heart rate = 95 (SR) - 105 (ST) b/min, N/I BP = 90 - 100 / 35 - 45, RR = 22 - 26 br/min, SpO2 = 88-90% (RA), Temp = 35.9°C. On physical exam, the patient was a middle-aged male appearing older than his stated age, and in apparent mild-to-moderate discomfort / distress, multiple tattoos over each arm, as well as the front of chest. His HEENT reveals (+) icteric sclera, (+) multiple spider angiomata over face, dried blood around mouth & nares, (+) severe gingivitis, (+) poor dentition w/ multiple broken, chipped & missing upper & lower teeth. The airway evaluation reveals MP class III with large tongue & partially obstructed uvula, < 6 cm thyromental distance. His neck had FROM, and (+) JVD 5 cm @ 45°. The chest exam was (+) for gynecomastia, and lungs with decreased bibasilar

breath sounds with diffuse rhonchi over upper lung fields. His heart was tachycardic, w/ an occasional extrasystole, normal S1 / S2, and (+) grade II over VI systolic flow murmur. The abdomen was distended with decreased bowel sounds, and non-tender. There was (+) caput medusa, (+) fluid wave, and large splenic edge. The rectal exam revealed an enlarged prostate gland with dark tarry, heme (+), & malodorous stool. His extremities demonstrated (+) moderate clubbing of nail beds on both hands, but no cyanosis. There was generalized muscle atrophy in both upper &lower extremities. He was awake, but very agitated and oriented only to person. The neurologic exam revealed (+) hand tremor, unsteady gait and balance while walking, (+) generalized decreased muscle strength & motor function elicited = 4 / 5 bilaterally.

The patient's available lab data included; WBC# = 2.9 k/dl, Hemoglobin (Hgb) = 7.5 gm/dl, Hematocrit (Hct) = 22.4 % and Platelets (PLTS #) = 35 k/dl. His basic metabolic profile *(BMP) demonstrated* Sodium = 127 mEq/L, Potassium = 3.1 mEq/L, Chloride = 88 mEq/L, Bicarbonate = 18 mEq/L, Blood Urea Nitrogen = 26 mg/dl, Creatinine = 0.4 mg/dl and Glucose = 55 mg/dl. The blood clotting studies found prothrombin time (PT) = 17.5 sec, INR = 2.3x, and activated partial thromboplastin time (aPTT) = 46 sec. The 12-Lead EKG and AP CXR are pending. You are now called to emergently intubate, because he has experienced a "massive episode of upper GI bleeding."

Questions for thought & reflection:

(Q1) How should the anesthesiologist respond to this situation, and manage the airway?
(Q2) What are some of the general pathophysiologic changes associated with ESLD?
(Q3) Why does the patient with ESLD usually have hyperdynamic, hypotensive (i.e., septic-like) cardiovascular parameters? How can this be optimized prior to any planned surgery?

After a very difficult oral intubation, the patient is paced on a mechanical ventilator with the following settings; SIMV mode, set RR = 10, Vt = 700 cc, FiO_2 = 0.50, PEEP = +5, and PS = +5 cm H20. Unfortunately, the SpO_2 does not rise above 89%, despite moving to an FiO_2 = 1.0.
(Q4) What is the etiology of Hepato-Pulmonary syndrome? Why does the patient with ESLD frequently present with oxygen refractory intra-pulmonary shunting? Describe the resultant clinical findings, as well as the underlying pathophysiologic mechanisms involved?
(Q5) How can the ventilator settings be adjusted to improve this patient's oxygenation status?

The surgery team plans to insert a Sengstaken-Blakemore (S-B) tube, and then prepare him for a porta-caval shunt procedure. The RN, however, informs you that the patient has been oliguric (i.e., 10 cc of urine past hour) since his arrival in the ICU.
(Q6) What is the etiology of Hepato-Renal syndrome? Why does the patient with ESLD frequently present with acute renal failure? Describe the resultant clinical findings, as well as the underlying pathophysiologic mechanisms involved?
(Q7) How can the patient with ESLD and Hepato-Renal syndrome be medically managed in order to be optimized prior to invasive procedures and/or planned surgery?

A right radial (#20g) A-line, and a right internal jugular venous (#8.5 fr) introducer catheter are inserted while still in the ICU. Four hours later, the patient is taken to the OR to undergo surgery. Approximately, 30 min after initial skin incision, you inform the surgeons that they have already lost 1,000 cc of blood, and counting. The surgeons reply that they have encountered

severe medical bleeding and oozing from all the cut surfaces. **(Q8)** How should the anesthesiology team monitor the status of this patient's hemostatic function? Describe the assessment of the coagulation system, and the fibrinolytic system?

(Q9) What are some of the new concepts related to our understanding of the pathophysiology & management of coagulopathy? Disseminated intravascular coagulation (DIC)?

(Q10) What are some of the advantages and/or disadvantages associated with massive transfusion in the critically ill patient? ESLD patient?

PROBLEM BASED LEARNING DISCUSSION

The initial approach to the patient with ESLD is highly complex, since frequently they present with multi-organ dysfunction syndrome (MODS). Of particular concern for the anesthesiologist asked to manage these patients are three distinct areas; (1) hepato-pulmonary syndrome, (2) hepato-renal syndrome, and (3) DIC / medical coagulopathy associated with massive hemorrhage. This PBLD session will attempt to focus on each of these issues with special emphasis placed on the pathophysiology, peri-op assessment and initial management strategies of these common entities. Although recent scientific breakthroughs and theories published in the medical literature may be discussed, special emphasis will be placed on providing practical information that will have obvious relevance to the clinician's daily practice. Moreover, every effort will be made to guide the discussion forward based on an in-depth analysis of the aforementioned case.

In the peri-op setting, the bleeding, ESLD patient presents unique challenges to the anesthesiologist and intensivist. A novice might conclude that simply transfusing large quantities of clotting factors (i.e., FFP) with platelets would eventually bring the hemorrhage under control. In addition, the use of vitamin K and/or ε-aminocaproic acid has often been thought to be helpful in resolving the underlying coagulopathy. Unfortunately, these approaches in, and of themselves, rarely prove successful. Therapeutic strategies that require resuscitation with "massive amounts" of blood and blood products usually don't work, and many times trigger a sequence of events that only exacerbate the hematologic derangements. Certainly, the peri-op physicians caring for these patients must be able to rapidly identify the cause of the hemorrhage, and distinguish between surgical and non-surgical bleeding. In the former case, the vessels which are the likely source of hemorrhage need to be identified. Whereas, in the latter instance, a rapid assessment of the patient's PMHx, physical, and lab studies must be undertaken to develop a differential diagnosis of medical bleeding. It is vital to identify any patient at increased risk of hemorrhage early in their peri-operative course.

In order to manage episodes of peri-operative hemorrhage associated with ESLD, the practitioner must first understand the normal *in vivo* function of the coagulation system. The role of the coagulation system includes; (1) maintenance of vascular integrity, (2) provision of effective hemostasis [i.e., if #1 is violated], and (3) avoid unnecessary clot formation and pathologic thrombosis. Although frequently taken for granted, normal hemostasis requires a delicate balance between the individual's ability to form an effective clot, and thereafter gradually dissolve it. The initial trigger of effective hemostasis hinges almost entirely on the circulating platelets (PLTS). This requires both adequate quantitative (i.e., number of PLTS) and qualitative (i.e., PLTS function) characteristics. Simultaneously, the intrinsic coagulation system becomes activated when exposed collagen from the damaged vascular endothelium comes into contact with high molecular weight kininogen (HMWK) and pre-kallikrein (PK) triggering

activation of factor XII to XIIa. In contrast, the extrinsic system responds when exposed tissue factor (i.e., phospholipid surfaces) in the vascular endothelium trigger activation of factor VII to VIIa. These both lead into the common pathway, in which factor Xa activates factor II (prothrombin) to IIa (thrombin) in the presence of Ca^{++}, factor Va, and platelet factor 3. Thrombin then cleaves factor I (i.e., fibrinogen) into fibrin, and factor XIIIa in the presence of Ca^{++} is able to polymerize these monomers into a fibrin mesh. This fibrin lattice is eventually integrated into the platelet plug and forms a stable clot.

The traditional model of coagulation is useful, and helps to explain the findings encountered in clinical practice, as well as on clotting studies (e.g., aPTT & PT tests). Unfortunately, it does not explain all of the observations seen in the clinical arena, nor does it account for every *in vivo* derangement encountered in a critically ill patient's hemostatic system. For example, the true function of the *intrinsic pathway* remains unclear, since deficiencies of factor XII, high-MW-kininogen, or pre-kallikrein do not, in and of themselves, result in clinical bleeding. Likewise, the lack of either factor VIII or IX will result in hemophilia, and the well described propensity for coagulopathy. Thus, we are left to conclude that distinct intrinsic and extrinsic cascades, although useful to our understanding, may not function independently under routine circumstances. What then does occur in vivo? Recent evidence has shown that factor VIIa-tissue factor complex is able to activate factor IX and X. In addition, activated PLTS can provide a surface for activation of factor XI by thrombin. These observations help to explain why factor XII, high-MW-kininogen, or pre-kallikrein may not always be necessary for intact hemostasis. Additionally, these findings have led to the development of a new model of hemostasis which incorporates the vital function of the cell surfaces into the process. Instead of describing hemostasis as a continuous flow of substrates through two parallel pathways, this theory centers around three distinct, but overlapping phases occurring on surfaces of two distinct cells; the activated PLT, and the tissue factor (TF)-bearing cell.

Severe, generalized bleeding in ESLD may result from many different etiologies. Some of these include; (1) dilutional thrombocytopenia, (2) thrombocytopathy (i.e., abnormal PLT function / non-dilutional), (3) iatrogenic coagulopathy (e.g., unfractionated heparin, LMW-heparin, & warfarin), (4) Severe, combined coagulopathy (e.g., DIC), (5) primary and secondary hypo-fibrinogenemia, (6) severe single factor deficiency, and/or (7) profound hypothermia. Any disorder that involves more than one of these elements will tend to produce more severe bleeding than if only one of these elements were abnormal. The term combined coagulopathy has been coined to describe such problems. Acquired, combined coagulopathies tend to be more difficult to diagnose and treat peri-operatively. The most important of these is DIC, a clinical syndrome which is not readily identified by any single laboratory test, and presents with a host of protean manifestations and etiologies. It may occur in any setting that predisposes to coagulopathy, and thus frequently co-exists with other ongoing pathologic derangement in hemostasis.

DIC results when generalized clotting and dissolution of clot take place within the microvasculature in an uncontrolled manner. This is usually initiated by holosystemic triggers of the clotting cascade. It is important to emphasize, however, that DIC is not a primary event, but rather reflects the ravages of another co-morbid process. The exact cellular processes involved in the development of DIC remain an area of intense research and debate. The unifying observation centers on the fact that tissue beds which experience a combination of stagnation of blood flow, relative hypoxia, and metabolic acidosis progressively release tissue-derived thromboplastin

(TTP) into the blood stream. The actual cascade seems to be triggered by; *(1) Intrinsic messenger signal / trigger* - release of TTP following severe closed head injury, prostate surgery, pulmonary contusion (lung injury), *(2) Extrinsic messenger signal / trigger* -endotoxin (gram negative sepsis), cell membrane proteins (gram positive sepsis), & tumor necrosis factor (malignancy). Once activated, the coagulation cascade rapidly consumes factors I, II, V & VIII, as well as large quantities of PLTS. Fibrin strands and micro-thrombi are deposited throughout the entire microcirculation of all vital organs which further reduces regional blood flow, and propagates the entire process. In a desperate attempt to counteract the hypercoagulable state, the body activates the fibrinolytic system to dissolve the fibrin mesh and retract the clot which heralds *secondary fibrinolysis.* Activation of plasminogen to plasmin occurs progressively more rapidly, so that plasmin can degrade fibrin and fibrinogen. This exacerbates the state of hypofibrinogenemia, and releases d-Dimer fragments and fibrin degradation products (FDP) into the systemic circulation. These compounds act not only as a marker of DIC, but may also help perpetuate the process. Over time, the fibrinolytic system becomes exhausted, while the amount & activity of tissue plasminogen activator (TPA), as well as plasmin rapidly decline. Microvascular coagulation then proceeds unopposed (i.e., a pre-terminal event), ultimately resulting in severe morbidity (i.e., multiple organ dysfunction syndrome [MODS] / multisystem organ failure [MSOF]), and mortality. A DIC-panel should be sent early in the patient's course, once clinical evidence of severe bleeding is observed. If DIC is present, then it will reveal; (1) ↓PLT count, (2) ↑aPTT (3) ↑PT / INR, (4) ↓Fibrinogen count, (5) ↑FDP / FSP, and ↑d-Dimer titer. If available, a TEG tracing should be obtained as soon as possible, and thereafter at hourly intervals until normalization of the hemostatic process occurs. This is likely to reveal both an abnormal quantitative (i.e., R, MA, Alpha [α] and kappa [κ] values) &/or qualitative pattern. From the preceding pages, it should be obvious that the entire process of hemostasis is extremely complex, and requires a delicate balance between two dialectical and opposing forces. On the one hand, the coagulation cascade initially attempts to maintain vascular integrity by creating PLT plugs to dam any disruption of the vessel wall. Thereafter, a complex process is triggered, which includes both cellular and humoral elements, and is aimed at reinforcing the tentative PLT plug with a flexible, yet resilient, fibrin-lattice mesh. Concurrently, the fibrinolytic system is activated and prepares for eventual modification and retraction of the clot, so that detrimental regional and/or systemic thrombosis can be avoided. Unfortunately, in such a complex system, even subtle perturbations may cause the system to go awry. This PBLD session will attempt to expand on the foregoing didactic material, and place special emphasis on new paradigms for understanding the basic science of coagulation and fibrinolysis as they relate to both the normal and abnormal states. Finally, this session aims to integrate the discussion in the framework presented by this case.

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LEARNING SUMMARY

Develop a basic understanding of the pathophysiology of end-stage liver disease; develop an appreciation of the pathophysiology, as well as the initial management of hepato-pulmonary and hepato-renal syndromes; develop a basic understanding of the diagnosis & pathophysiology of severe generalized (i.e., non-surgical) bleeding in adults; and develop an organized strategy for the management of disseminated intravascular coagulopathy with special emphasis on the rational use of blood & blood component therapy.